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Fryns Syndrome Phenotype and Trisomy 22

Jean-Marie Ladonne, Dominique Gaillard, Frédérique Carré-Pigeon, and René Gabriel

Departments of Gynecology and Obstetrics (J.-M.L., R.G.), and Developmental Pathology and Cytogenetics INSERM U314 (D.G., F.C.-G.), Hospital Maison Blanche, Reims, France

Trisomy 22 was detected in a 32-week-old fetus born to an overweight mother with hypertension. Severe intrauterine growth retardation was associated with phenotypic manifestations of Fryns syndrome: diaphragmatic hernia, facial defects, and nail hypoplasia with short distal fifth phalanges. This is the second report of congenital diaphragmatic hernia in trisomy 22. This case demonstrates the importance of karyotyping malformed fetuses or newborns, even if a nonchromosome syndrome seems identifiable on clinical grounds. To date, at least 10 cases of Fryns syndrome have been reported without chromosome analysis.

KEY WORDS: trisomy 22, Fryns syndrome, human chromosomes, multiple malformations, diaphragmatic hernia

INTRODUCTION

Trisomy 22 is rare in liveborn infants (1/30,000–1/50,000 live births) [Punnet et al., 1973]. This chromosome anomaly is more common in spontaneous abortions (2.9%) [Hassold, 1980]. The main clinical findings reviewed in recently published cases. [Petersen et al. 1987; Voiculescu et al., 1987; Vohra et al., 1987; Kukolich et al., 1989; Phillipson et al., 1990; Sundareshan et al., 1990; McPherson and Sterka, 1990; Isada et al., 1990; Ferret et al., 1991; Kim et al., 1992; Kobrynski et al., 1993; Stratton et al., 1993a] have been severe growth retardation; facial defects including frontal bossing, hypertelorism, broad nasal bridge, epicanthic folds, downslanting palpebral fissures, abnormal and apparently low-set ears, preauricular tags or pits, cleft lip or palate, and microretrognathia; congenital heart defect; hypoplastic nails and phalanges; mental retardation; and early death. Before using multiple banding techniques and examining more than one tissue, the existence of complete trisomy 22 in liveborn infants was debated [Schinzel, 1981]. Here we report a new case confirmed by banding techniques in a patient with diaphragmatic hernia and several clinical manifestations described in Fryns syndrome, a sublethal condition with autosomal-recessive inheritance [Fryns et al., 1979; Fryns, 1987]. This case report confirms once more the necessity of chromosome analysis in malformed fetuses or newborns, even when a nonchromosomel syndrome appears to be identifiable.

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Address reprint requests to Pr. Dominique Gaillard, Department of Developmental Pathology, Hospital Maison Blanche, INSERM U314 45 rue Cognacq Jay, 51092 Reims Cedex, France.

CLINICAL REPORT

The proposita was the second child born to a healthy although overweight 38-year-old G3P2 mother and a 42-year-old father. The parents were nonconsanguineous, and their previous child is normal. The pregnancy was early complicated by diabetes and hypertension (11 weeks). A high degree of intrauterine growth retardation, thought to be related to toxemia, was detected by ultrasonography at 24 weeks of gestation when the mother was referred for amniocentesis because of advanced age. Unfortunately, no cells grew from the amniotic fluid. Because of the high degree of obesity of the mother, no cordocentesis could be planned, and no ultrasonographic details were detected. She was delivered by cesarean section at 32 weeks of gestation because of eclampsia. Birth weight was 945 g (−2 SD), length 36 cm (−1 SD), and head circumference (OFC) 25 cm (−2 SD). The Apgar score was 3 at 1 min. Respiratory sounds were diminished on the left side, and heart sounds were shifted to the right side, raising suspicion of congenital diaphragmatic hernia. Ventilary support was stopped, as it failed to improve respiratory distress, and the infant died a few minutes after birth.

Noted on physical examination were micrognathia, macrostomy, cleft lip on the left and complete cleft palate, long upper lip (Fig. 1), small and apparently low-set malformed ears with marked overfolding of the helix, and bilateral preauricular depression. There were bilateral epicanthal folds, flat nasal bridge with short nose, and downslanting of the palpebral fissures. Limb anomalies included hypoplastic distal phalanges, hypoplastic nails on the four first fingers and toes with total absence of last finger- and toenails (Fig. 2), clinodactyly of the fifth fingers, and clubfeet with prominent

Fig. 1. Face of patient at postmortem examination. Note cleft lip, macrostomy, broad nasal bridge, large forehead, and micrognathia.

Fig. 2. Hand of patient at postmortem examination. Note severe nail hypoplasia.

heels. Palmar creases were normal. Skeletal roentgenograms detected absence of the distal phalanges of the right fifth finger and hypoplastic left fifth finger. When examining the genitalia it was difficult to determine the true sex of the fetus, which was considered a female with overdevelopment of the vulva, until cytogenetic study showed a Y chromosome.

Autopsy demonstrated a large left diaphragmatic hernia, with hypoplastic lungs shifted to the right. Herniated in the left hemithorax were the left part of the liver, the caecum with the appendix, the distal part of the small intestine, and the spleen. As a result of the diaphragmatic hernia, there was mesenteric malfixation and a globular pancreas.

Heart examination showed a tetralogy of Fallot with atresia of the pulmonary valve (diameter 1 mm), dextroposition of a large aorta (diameter 6 mm), hypertrophy of the right ventricle, and a high perimembranous ventricular septal defect (diameter 6 mm). The kidneys were hypoplastic and showed a multicystic dysplasia. The bladder was small. Study of the brain demonstrated absence of olfactory bulbs. No gonads were found in the pelvis or in the abdomen. The placenta was hypotrophic (240 g) and showed distal immature villi embedded in fibrin with calcifications. The fetal vessels were dilated and included a few erythroblasts. Most of the villi showed trophoblastic nuclear knots.

Chromosome analysis was performed on PHA-stimulated lymphocytes from peripheral blood and on skin fibroblasts. All 20 R-banded cells examined showed a modal number of 47 chromosomes with an extra chromosome 22:(47,XY,122). Both parents showed normal chromosomes.

DISCUSSION

Trisomy 22 was ascertained in a polymalformed newborn infant with intrauterine growth retardation, diaphragmatic hernia, facial defects, heart defects, and distal phalange and nail hypoplasia. Before chromosome analysis, growth retardation was attributed to toxemia and hypertension, while the association of diaphragmatic hernia with facial anomalies and nail hypoplasia led to a diagnosis of Fryns syndrome.

Diaphragmatic hernia has only been reported in one case of trisomy 22 [Kim et al., 1992], and was associated with growth retardation and multiple anomalies including microcephaly, absence of corpus callosum, and webbed neck. Unlike Kim et al. [1992], we found no association with corpus callosum agenesis, but arhinencephaly was detected and associated with cleft palate and cleft lip. However, these two anomalies are part of the same developmental field.

If we compare he clinical manifestations of trisomy 22 with those of Fryns syndrome, the main differences appear in growth, which is normal in Fryns syndrome (60% of cases at the 50th centile, and only 3 cases <5th centile [Aymé et al., 1989; Goddeeris et al., 1980; Cunniff et al., 1990], and always very retarded in trisomy 22 (100% of cases <5th centile). The presence of diaphragmatic hernia is exceptional in trisomy 22 and present in >80% of reported cases of Fryns syndrome [Samueloff et al., 1987; Schwyzer et al., 1987; Moerman et al., 1988; Bamforth et al., 1989; Cunniff et al., 1990; Krassikoff and Sekhon, 1990; Kershisnik et al., 1991; Bulas et al., 1992; Hanssen et al., 1992; Stratton et al., 1993b]. The following clinical abnormalities can be detected in both syndromes with a high frequency:

"coarse" face, broad nasal bridge, retromicrognathia, abnormal ears, distal digital hypoplasia, nail hypoplasia, and genital anomalies. Many manifestations of Fryns syndrome were also found to be associated with mosaicism for isochromosome 12p in Pallister-Killian syndrome [Bergoffen et al., 1993; McPherson et al., 1993].

To date, 10 Fryns syndrome cases have been reported without chromosome analysis [Fryns et al., 1979; Lubinsky et al., 1983; Aymé et al., 1989; Samueloff et al., 1987; Bamforth et al., 1989; Cunniff et al., 1990; Hanssen et al., 1992], and one of these showed intrauterine growth retardation associated with left cleft lip, cleft palate, hypoplasia of all phalanges, left diaphragmatic hernia, severe bilateral lung hypoplasia, malfixation of the mesentere large auricular septal defect, cystic right kidney, and normal brain [Aymé et al., 1989].

This evidence suggests that before confirming the diagnosis of Fryns syndrome, trisomy 22, as well as mosaicism for i(12p), should be ruled out, in order to facilitate appropriate genetic counselling.

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